BMJ

BMJ 2012;344:e289 doi: 10.1136/bmj.e289 (Published 7 February 2012)

CLINICAL REVIEW

Diagnosis and management of Raynaud's phenomenon

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Raynaud's phenomenon is caused by episodic vasospasm and ischaemia of the extremities in response to cold or emotional stimuli, which result in a characteristic triphasic colour change in extremities—usually fingers or toes—from white, to blue, to red. Raynaud's phenomenon may be primary, in direct response to stimuli, or secondary to an underlying condition. In 10-20% of cases it may be the first presentation of, or may precede the onset of, a connective tissue disease (such as scleroderma or mixed connective tissue disease), so that underlying causes must be ruled out.

Raynaud's phenomenon is triggered by a change in temperature rather than simply exposure to cold. Patients can have attacks throughout the year—for example, if they move from a warm environment to an air conditioned one, stand in a cold wind (even on a relatively warm day), or hold a cold milk bottle.[1]

A recent consensus statement on terminology produced by the vascular medicine section of the Royal Society of Medicine recommended abandoning the terms Raynaud's syndrome and Raynaud's disease because of the lack of consensus on their use (Raynaud's phenomenon: new insights, new treatments. Conference organised by the Vascular Medicine Section of the Royal Society of Medicine. 2011 May). In this review we refer to primary and secondary Raynaud's phenomenon. Recent advances in the management and treatment of this phenomenon have followed on from the findings of randomised controlled trials of treatment strategies. We review observational studies, randomised controlled trials, systematic reviews, and guidelines to provide an overview of the clinical presentation of Raynaud's phenomenon, its risk factors, its diagnosis, and the current and potential treatments.

Who gets Raynaud's phenomenon?

The prevalence of Raynaud's phenomenon varies widely across countries and populations. Non-population based studies of prevalence show that 3-12.5% of men and 6-20% of women report symptoms of Raynaud's phenomenon. The average age of onset is lower in women than in men, and prevalence is higher in colder climates.[2] Family history, oestrogen exposure, and emotional stress are commonly associated with the phenomenon in women, whereas smoking and hand arm vibration syndrome (HAVS[3]) are more commonly implicated in men.[2] Information from the Raynaud's and Scleroderma Association states that smoking reduces body temperature by 1°C over 20 minutes.[4]

Many conditions have been associated with secondary Raynaud's phenomenon (box 1), most notably systemic sclerosis and mixed connective tissue disorders. An observational study of about 1500 people found that 89% of Raynaud's phenomenon was classified as primary and 11% as secondary.[5] Around 12.5% of patients with Raynaud's phenomenon develop scleroderma and 13.6% develop connective tissue diseases.[6]

What are the symptoms?

Patients with Raynaud's phenomenon classically report intermittent triphasic changes in the colour of the extremities (fingers, toes, nose, cheeks, and ears)—usually triggered by cold exposure or emotional stress—from white (owing to vasoconstriction), to blue (tissue hypoxia), to red on rewarming (reperfusion) (figs 1⇓ and 2⇓). Colour changes are associated with tightness in the first two stages and burning pain in the reperfusion stage. Not all of the three phases are needed to make a diagnosis.[7] Colour changes occur intermittently and tend to resolve when the digits are rewarmed. An attack may last for minutes to hours. Patients with secondary Raynaud's phenomenon are more likely to have severe disease, which, if left untreated, can progress to ulceration or gangrene of extremities.

What causes Raynaud's phenomenon?

The pathophysiology of Raynaud's phenomenon is poorly understood and is thought to differ between primary and secondary disease. A recent review discussed pathogenesis.[8] Abnormalities of the blood vessel wall are thought to be functional in primary Raynaud's phenomenon and structural in secondary disease. Abnormalities of neural control mechanisms are considered less likely to be important in the pathogenesis of primary Raynaud's phenomenon. Intravascular factors—such as platelet activation, defective fibrinolysis, reduced red blood cell deformability, and increased blood viscosity—are associated with secondary Raynaud's phenomenon, whereas white blood

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Extra references supplied by the author (see http://www.bmj.com/content/344/bmj.e289?tab=related#webextra)

Summary points

- Raynaud's phenomenon is caused by episodic vasospasm and ischaemia of the extremities, particularly the digits, in response to cold or emotional stimuli
- Attacks comprise a colour change in extremities from white (ischaemia), to blue (deoxygenation), and then to red (reperfusion)
- Primary Raynaud's phenomenon is an exaggerated response to stimuli, with no known underlying cause
- Secondary Raynaud's phenomenon is usually caused by connective tissue disease and patients are more likely to develop tissue damage
- Nifedipine is currently the only drug licensed for use in Raynaud's phenomenon
- Key areas of ongoing research include a topical nitroglycerin and a rho kinase inhibitor (vasodilator)

Sources and selection criteria

We searched the Cochrane Library and PubMed (2001-11) using the term "Raynaud's". Recommendations made at the May 2011 conference "Raynaud's phenomenon: new insights, new treatments" organised by the vascular medicine section of the Royal Society of Medicine were reviewed. We also consulted published guidelines and information from the European League Against Rheumatism, Raynaud's and Scleroderma Association, and Arthritis Research UK.

Box 1 Conditions associated with secondary Raynaud's phenomenon

Rheumatological

- Systemic sclerosis (90% of patients with this condition have Raynaud's phenomenon)
- Mixed connective tissue disease (85%)
- Systemic lupus erythematosus (40%)
- Dermatomyositis or polymyositis (25%)
- Rheumatoid arthritis (10%)
- Sjögren's syndrome
- Vasculitis

Haematological

- Polycythaemia ruba vera
- Leukaemia
- Thrombocytosis
- Cold agglutinin disease (Mycoplasma infections)
- Paraproteinaemias
- Protein C deficiency, protein S deficiency, antithrombin III deficiency
- Presence of the factor V Leiden mutation
- Hepatitis B and C (associated with cryoglobulinaemia)

Occlusive arterial disease

- External neurovascular compression, carpal tunnel syndrome, and thoracic outlet syndrome
- Thrombosis
- Thromboangiitis obliterans
- Embolisation
- Arteriosclerosis
- Buerger's disease

cell activation and oxidative stress have been reported in primary and secondary disease. The key to appropriate treatment lies in understanding the underlying mechanism, but there is still some way to go before a clear understanding is able to inform a gold standard treatment.[8]

How are patients with Raynaud's phenomenon assessed?

Raynaud's phenomenon is diagnosed clinically.

History

Ask patients about the frequency and pattern of colour changes, which stage(s) they experience, which digits are affected, associated features such as pain and changes in sensation, what triggers an attack, and what relieves it. A symptom diary can help to produce a clear picture of attacks. Encourage patients to photograph the affected extremities during an attack.

A full systemic inquiry will detect secondary causes (box 2). Key questions to ask include whether the patient has any evidence of a rash, photosensitivity, migraines, joint pains, ulcers, dysphagia, and xerostomia. Occupations of note are those involving cold exposure and vibrating tools. If employers do not help facilitate reduced exposure to vibrating tools, patients may be entitled to compensation under the Control of Vibration at Work Regulations 2005.[9] Ask about drugs that may predispose patients to the phenomenon or aggravate it: β blockers, vinyl chloride, chemotherapy, ergot derivatives, amphetamines, cocaine, oestrogen (unopposed oestrogen replacement therapy, oral contraceptives), clonidine, and sympathomimetics. Also ask about current smoking because smoking aggravates the condition.

Box 2 Distinguishing primary and secondary Raynaud's phenomenon

Primary disease

- Younger age (<30, but can be any age)
- Female
- Genetic component (30% have an affected first degree relative[5])
- No symptoms/signs of underlying disease
- No tissue necrosis or gangrene
- Normal nail fold capillaries
- Normal erythrocyte sedimentation rate
- Negative antineutrophil antibodies

Secondary disease

- Older age (>30, but can be any age)
- Less common (10-20%)
- Symptoms and signs of underlying disease
- Tightness of finger skin; more severe pain
- Digital ischaemia (digital pitting scars, ulceration, or gangrene)
- Abnormal nail fold capillaries
- Raised erythrocyte sedimentation rate
- Positive antineutrophil antibodies or anti-extractable nuclear antigen antibodies

The Raynaud's condition score (box 3) is an ordinal score from 0-10 that measures the level of difficulty experienced by patients; it may help determine the impact of the condition on the patient's functioning.

Examination (look, feel, move)

Examination may be tailored according to clues from the history.

In the hands look for colour changes, nail bed changes, and skin integrity. Sclerodactyly, flexion deformities, tendon friction rubs, and calcinosis are seen in systemic sclerosis.

Digital ulcerations (fig 3⇓) are not normal and always reflect secondary Raynaud's phenomenon; they should prompt careful examination for other signs of connective tissue disease and referral to a specialist.

Feel for peripheral pulses. Synovitis suggests an inflammatory arthropathy.

Move all joints and assess for pain and contracture.

In the face look for a malar rash, non-scarring alopecia, and oral ulcers, which may suggest systemic lupus erythematous, and for tightening of the skin, which is indicative of systemic sclerosis.

Identify any dry skin, telangiectasia, and the salt and pepper appearance of hyperpigmentation and hypopigmentation, which are indicative of systemic sclerosis. Also look for livedo reticularis, which suggests systemic lupus erythematous or antiphospholipid syndrome.

Assess for arrhythmias, especially atrial fibrillation and murmurs, which provide evidence of thromboembolic disease (or rarely Libman-Sacks endocarditis). Pulmonary fibrosis suggests systemic sclerosis.

Investigations

Patients with primary Raynaud's phenomenon do not routinely need blood tests.

Patients with a clinical suspicion of secondary Raynaud's phenomenon should have a full blood count to look for anaemia and lymphopenia, which suggest an underlying autoimmune disease; immunology tests for antinuclear antibodies (ANA), extractable nuclear antibodies (ENA), anti Scl-70 (topoisomerase I), anti-Ro (SS-A), and anti-La (SS-B); inflammatory markers such as erythrocyte sedimentation rate and plasma viscosity. Negative results cannot exclude a secondary cause.

Patients with unilateral signs should have a chest radiograph to look for a cervical rib compressing the bronchial and cephalic vascular branches. Perform magnetic resonance imaging if thoracic outlet syndrome is suspected.

Specialist investigations performed in secondary care include infrared thermography, laser Doppler flowmetry, portable radiometry, and digital plethymography, all of which highlight a pattern of changes consistent with scleroderma (box 4). The results of these are often analysed together with a cold stimulation test, which measures the response of the digits to cooling and rewarming. Digits usually rewarm in less than 15 minutes, but in Raynaud's phenomenon this phase is longer than 20 minutes.

Refer patients with suspected secondary disease for capillaroscopy if possible because ophthalmoscopy (20× magnification, dermatoscope 10× magnification) can miss capillary changes. The gold standard method is videocapillaroscopy (200× magnification, or a biomicroscope). A patient with primary Raynaud's phenomenon will have regular disposition of capillary loops along the nail bed. In contrast, patients with secondary disease will have architectural disorganisation, giant capillaries, haemorrhages, loss of capillaries, angiogenesis, and avascular areas ("scleroderma pattern," seen in 95% cases of systemic sclerosis).[10] Around 80% of patients with Raynaud's phenomenon, scleroderma antibodies, and a scleroderma pattern on capillaroscopy will develop scleroderma after 15 years, but if capillaroscopy is normal the likelihood of developing scleroderma is almost nil.[6]

Capillaroscopy is now part of the new definition for early systemic sclerosis proposed by the European League Against Rheumatism (EULAR).[11]

When and who to refer?

Most patients can be managed in primary care. However, referral (usually to a rheumatologist) should be considered if:

- The diagnosis is in doubt
- A secondary cause is suspected

Box 3 Raynaud's condition score[w7]

The patient is asked about the frequency, duration, and severity of attacks to arrive at a single score expressed on a scale of 0-10 (0=patient not handicapped by attacks; 10=patient extremely handicapped).

Questions

How many attacks have you had today**?**

How long did they last?

How much pain, numbness, or other symptoms have you had today?

How much has Raynaud's affected the use of your hands today?

Box 4 Specialist secondary care investigations

Infrared thermography

Detects infrared energy emitted from skin, converts it to temperature, and displays an image of temperature distribution

Laser Doppler flowmetry

A non-invasive continuous measure of microcirculatory blood flow that uses monochromatic light emitted from a low power laser

Portable radiometry

Measures the temperature at the centre of the whorl of the palmar aspect of each fingertip

Digital plethymography

Air pressures that occur in a sensing cuff applied to the finger are amplified and filtered to make it possible to measure arterial blood flow

- The cause is thought to be job related (refer to occupational health services)
- The patient is aged under 12 years
- Digital ulcerations are present
- The symptoms are poorly controlled, despite appropriate conservative management.

How is Raynaud's phenomenon treated?

The first step in managing Raynaud's phenomenon in primary care is lifestyle modification. Such advice can be given to patients while awaiting investigations and referral to secondary care if an underlying cause is suspected. Most people with primary Raynaud's phenomenon respond well to lifestyle measures and need no further treatment. Patients with secondary Raynaud's phenomenon require treatment of the underlying disorder, which entails referral to secondary care.

Non-drug based treatments

Conservative approaches to treatment aim to reduce exposure to triggers, such as cold and emotional stress.

Advise the patient to try to keep warm, perhaps by using hand and feet warmers, which are commercially available. The frequency and severity of attacks can be reduced by avoiding dramatic changes in environmental temperature and taking steps to reduce occupational cold exposure. Vasodilation can be increased during attacks by rotating the arms in a windmill pattern, placing the hands under warm water or in a warm body fold such as the axilla, and performing the swing-arm manoeuvre (raising both arms above the shoulders and forcefully swinging them across the body to generate a force that promotes blood flow distally to the fingers).[12] Another simple tip is to avoid carrying bags by the handles, which impairs circulation to the fingers.[4] There is little objective evidence to suggest that any nutritional supplement benefits patients with the condition. Minimising stress through general relaxation techniques may be of benefit. Biofeedback has been a popular treatment, but a recent Cochrane review found it to be no more effective than sham biofeedback.[13] Support groups can provide helpful tips and guidance on self management. A prospective study showed that smoking cessation may help to reduce the severity but not occurrence of the condition.[14]

Ginkgo biloba has been investigated over the past 10 years. A double blind placebo controlled trial found a 56% reduction in the frequency of attacks in established Raynaud's phenomenon (compared with a 27% reduction in the placebo group).[15] Another randomised multicentre flexible dose open trial found a 31% reduction compared with 50.1% for nifedipine, suggesting that Ginkgo may not be as effective as nifedipine.[16] However, given that Ginko had no adverse effects and was well tolerated, further research may be worthwhile.

Drug treatments

Several randomised controlled trials are under way that may lead to an increase in the number of treatments for Raynaud's phenomenon. However, to date, no guidelines have been published on the medical treatment of Raynaud's phenomenon. We discuss drugs that are currently used off-label in the treatment of this condition and which the clinician may consider using on a case by case basis, taking care to balance evidence on efficacy versus toxicity. It is also important to review prescription drugs that aggravate symptoms.

Vasodilators

Calcium channel blockers—Non-cardioselective dihydropyridine calcium channel blockers are most widely used in the treatment of Raynaud's phenomenon. Nifedipine promotes relaxation of vascular smooth muscle cells and leads to vasodilatation. A meta-analysis of randomised controlled trials found that nifedipine (10-20 mg three times daily) reduced the number of attacks by 2.8-5.0 a week and reduced their severity by 33%. However, effects may be short lived, and longer acting calcium channel blockers or amlodipine and diltiazem may be needed.[17] Unfortunately, patients commonly report troubling adverse effects such as hypotension, flushing, headache, and tachycardia, so alternative treatments have been researched.

Topical nitrates—A randomised controlled study of 33 patients found that topical glyceryltrinitrate applied to the dorsum of the finger resulted in digital vasodilatation with fewer systemic side effects than with oral nitrates.[18] Two large recent randomised controlled trials of MQX-503, a new formulation of

nitroglycerin, applied to the affected finger found that it reduces the severity of Raynaud's phenomenon, but not the duration or frequency of attacks.[19 20] Evidence on topical nitrates is limited, but the results of current trials may provide more robust evidence of efficacy.

Prostaglandins—Prostaglandins have vasodilatory and antiproliferative effects, and they inhibit platelet aggregation. Their side effects are similar to those of calcium channel blockers. The European League Against Rheumatism recommends prostaglandins when calcium channel blockers have failed.[21] Most published studies have focused on the use of intravenous iloprost. A randomised open label single centre study and a 2009 Cochrane review found that iloprost reduces the frequency and severity of attacks.[22 23] A randomised study found cyclic use to be beneficial in terms of patient adherence and quality of life.[24] However, two randomised controlled trials found that iloprost was only slightly better than nifedipine,[25] and because iloprost is more expensive, the European League Against Rheumatism has advised that nifedipine should remain the first line drug for patients with Raynaud's phenomenon. A double blind multicentre placebo controlled study and randomised double blind study found that orally administered prostaglandins are less effective than intravenous ones, although higher doses may confer benefit.[21] Research is currently ongoing into the use of treprostinil, an oral prostaglandin analogue.

Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, and vardenafil)—Phosphodiesterase type 5 breaks down cGMP in endothelial cells. Inhibition of this enzyme increases the amount of cGMP available to promote vascular smooth muscle relaxation and blood flow. A randomised double blind placebo controlled fixed dose crossover study and two case series found a decrease in the frequency and severity of attacks in patients treated with oral sildenafil but not tadalafil compared with placebo. These inhibitors also have a favourable effect on the Raynaud's condition score and ulcer healing.[26-28] The benefits of these orally delivered and well tolerated drugs suggest that they may be an effective treatment for patients with severe and disabling Raynaud's phenomenon, although further studies are needed.

Antioxidants—N-acetylcysteine acts as a vasodilator via modulation of the vasodilator adrenomedullin. A recent observational study found that it decreases the frequency and severity of attacks. The number of digital ulcers and ulcer healing also improved.[29 30]

Inhibitors of vasoconstriction

Angiotensin receptor antagonists—A randomised controlled trial suggested that losartan reduces the frequency and severity of attacks to a greater extent than nifedipine.[31] The European League Against Rheumatism recommends its use, but this is an informal recommendation because of the lack of sufficient evidence.

Angiotensin converting enzyme inhibitors—These drugs are no longer recommended since a randomised double blind placebo controlled trial found that they do not reduce digital ulcers or the frequency or severity of attacks.[32]

α1 adrenoceptor blockers—Limited low level evidence from a randomised double blind placebo controlled crossover study of 24 patients suggests that prazosin may reduce the frequency but not the severity of attacks compared with placebo. However, prazosin is rarely used in the treatment of Raynaud's phenomenon because its potential adverse effects outweigh any benefit.[33]

Endothelin receptor antagonists (bosentan)—Endothelin is a potent vasoconstrictor of vascular smooth muscle cells. Among its other actions, bosentan exerts a consistent effect on vasculature. The Randomized Placebo-controlled Investigation of Digital Ulcers in Scleroderma (RAPIDS-1 and 2) trials have shown that the number of new digital ulcers in patients with secondary Raynaud's phenomenon decreased significantly when treated with bosentan.[21] The European League Against Rheumatism recommends its use when symptoms are refractory to treatment with calcium channel blockers and prostaglandins.

Serotonin reuptake inhibitors—The exact role of serotonin reuptake inhibitors in the treatment of Raynaud's phenomenon is not yet clear. These agents block the uptake of serotonin, which is a vasoconstrictor. A pilot study of 53 patients showed that fluoxetine reduces the severity and frequency of attacks compared with nifedipine in primary Raynaud's phenomenon. Its effect in secondary Raynaud's phenomenon was less pronounced.[w1] A Cochrane review of a small number of studies concluded that another serotonin reuptake inhibitor, ketanserin, was not beneficial in the treatment of Raynaud's phenomenon.[w2] This agent may have a role in patients who cannot tolerate other drugs because of hypotension, but more research is needed.

Botulinum toxin A—Botulinum toxin A blocks vasoconstriction and, although there are no blinded placebo trials to date, preliminary reports have suggested that it can improve symptoms, decrease frequency of attacks, and improve healing of digital ulcers.[w3 w4]

Others

Statins—After the observation that statins affect endothelial function, a 2008 randomised trial compared atorvastatin and placebo in patients with Raynaud's phenomenon associated with systemic sclerosis. Treatment with atorvastatin reduced the number of digital ulcers compared with placebo. Endothelial markers of activation also improved compared with placebo.[w5]

Aspirin—Although there is no firm evidence to support its use in patients with Raynaud's phenomenon, daily aspirin is commonly prescribed for patients who have no contraindications.

Does surgery have a role in treatment?

For a small number of patients with severe and disabling symptoms surgical intervention may be considered. Surgical interventions include arterial reconstruction, peripheral sympathectomy, embolectomy, and ulcer debridement, or a combination of techniques.

Cervical sympathectomy is no longer recommended because observational studies showed that it was not effective in the long term and that side effects were intolerable—patients often needed digital amputation. A therapeutic study with grade III evidence study found that digital artery (palmar) sympathectomy can lead to complete healing and a decrease in the number of ulcers, although it is a highly specialised procedure and this benefit is not seen for chronic digital ischaemia.[w6] Decompression arteriolysis and arterial reconstruction can be performed at the same time.

In chronic ulceration and in critical digital ischaemia, surgical debridement may reduce the need for amputation if osteomyelitis develops.

Contributors: All authors contributed equally to the writing of this article. AM and BG are guarantors. Thanks to April Lauren Rose Goundry

Tips for the non-specialist

- Examine patients with troublesome Raynaud's phenomenon carefully, looking for an underlying condition, although 80-90% will have no identifiable cause
- Offer conservative management options to everyone, even those awaiting referral or investigations; these include avoidance of stress and cold, smoking cessation, and ensuring that extremities are kept warm
- Nifedipine is the only drug licensed for use; other effective treatments are used off-label and are best prescribed by a specialist
- Refer patients with possible underlying disease, those who present with ulceration or signs of ischaemic digits, and those whose symptoms do not improve on treatment with a calcium channel blocker to a specialist

Ongoing research

- Trials are currently testing rho kinase inhibitors as a method of vasodilation
- MQX-503 (nitroglycerin) shows potential in reducing the severity of Raynaud's phenomenon
- Preliminary reports suggest that botulinum toxin A improves symptoms, reduces the frequency of attacks, and improves the healing of digital ulcers
- Oral phosphodiesterase type 5 inhibitors may be effective in patients with severe and disabling Raynaud's phenomenon, although further studies are needed

Additional educational resources

Resources for healthcare professionals

- Kowal-Bielecka O, Landewé R, Avouac J, Chwiesko S, Miniati I, Czirjak L. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009;68:620-8
- Raynaud's and Scleroderma Association (www.raynauds.org.uk/images/stories/PDF/hpbooklet2011.pdf)—Contains information on Raynaud's phenomenon and scleroderma for patients and healthcare professionals
- Herrick A. Raynaud's phenomenon. *Curr Treat Options Cardiovasc Med* 2008;10:146-55
- Levien TL. Advances in the treatment of Raynaud's phenomenon. *Vasc Health Risk Manage* 2010;6:167-77
- Baumhäkel M, Böhm M. Recent achievements in the management of Raynaud's phenomenon. *Vasc Health Risk Manage* 2010;6:207-14
- Bakst R, Merola JE, Franks AG Jr, Sanchez M. Raynaud's phenomenon: pathogenesis and management. *J Am Acad Dermatol* 2008;59:633-53

Resources for patients

- Raynaud's and Scleroderma Association (www.raynauds.org.uk)—Information for patients and healthcare professionals
- Arthritis Research UK (www.arthritisresearchuk.org)—Information leaflets for patients
- Patient.co.uk (www.patient.co.uk/health/Raynaud's-Phenomenon-(Cold-Hands).htm)—Information for patients on Raynaud's phenomenon
- Health and safety executive (www.hse.gov.uk/vibration/hav/index.htm)—Information on claiming compensation for hand and arm vibration syndrome
- International scleroderma network (www.sclero.org)—Comprehensive information on Raynaud's phenomenon, particularly when related to scleroderma; includes recent evidence based references, photographs, patient stories, and tips

(fourth year medical student), who helped to edit and proofread this review article.

Funding: No special funding received.

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

Patient consent obtained.

1 Reynaud's and Scleroderma Association. Coping with Raynaud's. www.raynauds.org.uk/raynauds/coping-with-raynauds.
2 Fraenkel L. Raynaud's phenomenon: epidemiology and risk factors. *Curr Rheumatol Rep* 2002;4:123-8.
3 Palmer K, Griffin M, Syddall H, Pannett B, Cooper C, Coggon D. Prevalence of Raynaud's phenomenon in Great Britain and its relation to hand transmitted vibration: a national postal survey. *Occup Environ Med* 2000;57:448-52.
4 Reynaud's and Scleroderma Association. Digital ulcers. www.raynauds.org.uk/component/content/article/138.
5 Riera G, Vilardell M, Vaqué J, Fonollosa V, Bermejo B. Prevalence of Raynaud's phenomenon in a healthy Spanish population. *J Rheumatol* 1993;20:66-9.
6 Koening M, Joyal F, Fritzler M, Roussin A, Abrahamowicz M, Boire C, et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis. *Arthritis Rheum* 2008;58:3902-12.
7 Wigley F. Raynaud's phenomenon. *N Engl J Med* 2002;347:1001-8.
8 Herrick AL. Pathogenesis of Raynaud's phenomenon. *Rheumatology (Oxford)* 2005;44:587-96.
9 Health and Safety Executive. Control of vibration at work regulations 2005. www.hse.gov.uk/vibration/hav/regulations.htm.
10 Herrick AL, Cutolo M. Clinical implications from capillaroscopic analysis in patients with Raynaud's phenomenon and systemic sclerosis. *Arthritis Rheum* 2010;62:2595-604.
11 Avouac J, Mogavero G, Guerini H, Drapé J, Mathieu A, Kahan A, et al. Predictive factors of hand radiographic lesions in systemic sclerosis: a prospective study. *Ann Rheum Dis* 2011;70:630-3.
12 Bakst R, Merola JE, Franks AG Jr, Sanchez M. Raynaud's phenomenon: pathogenesis and management. *J Am Acad Dermatol* 2008;59:633-53.
13 Malefant D, Catton M, Pope JE. The efficacy of complementary and alternative medicine in the treatment of Raynaud's phenomenon: a literature review and meta-analysis. *Rheumatology (Oxford)* 2009;48:791-5.
14 Suter LG, Murabito JM, Felson DT, Fraenkel L. Smoking, alcohol consumption, and Raynaud's phenomenon in middle age. *Am J Med* 2007;120:264-71.
15 Muir AH, Robb R, McLaren M, Daly F, Belch JJ. The use of Ginkgo biloba in Raynaud's disease: a double-blind placebo-controlled trial. *Vasc Med* 2002;7:265-7.
16 Choi WS, Choi CJ, Kim KS, Lee JH, Song CH, Chung JH, et al. To compare the efficacy and safety of nifedipine sustained release with Ginkgo biloba extract to treat patients with primary Raynaud's phenomenon in South Korea; Korean Raynaud study (KOARA study). *Clin Rheumatol* 2009;28:553-9.
17 Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford)* 2005;44:145-50.
18 Anderson ME, Moore TL, Hollis S, Jayson MI, King TA, Herrick AL. Digital vascular response to topical glyceryl trinitrate, as measured by laser Doppler imaging, in primary Raynaud's phenomenon and systemic sclerosis. *Rheumatology (Oxford)* 2002;41:324-8.
19 Chung L, Shapiro L, Fiorentino D, Baron M, Shanahan J, Sule S. MQX-503, a novel formulation of nitroglycerin, improves the severity of Raynaud's phenomenon: a randomized, controlled trial. *Arthritis Rheum* 2009;60:870-7.
20 Belch J, Fiorentino D, Denton C, Herrick A, Sule S, Steen V, et al. MQX-503, a novel topical nitroglycerin formulation, improves severity of symptoms associated with Raynaud's phenomenon [abstract]. *Arthritis Rheum* 2008;58(9 suppl):S622.

21 Kowal-Bielecka O, Landewé R, Avouac J, Chwiesko S, Miniati I, Czirjak L. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009;68:620-8.
22 Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells GA, et al. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev* 2000;2:CD000953.
23 Kawald A, Burmester GR, Huscher D, Sunderkotter C, Riemerkasten G. Low versus high-dose iloprost therapy over 21 days in patients with secondary Raynaud's phenomenon and systemic sclerosis: a randomized, open, single-center study. *J Rheumatol* 2008;35:1830-7.
24 Milio G, Corrado E, Genova C, Amato C, Raimondi F, Almasio PL, et al. Iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis and the quality of life: a new therapeutic protocol. *Rheumatology* 2006;45:999-1004.
25 Scorza R, Caronni M, Mascagni B, Berruti V, Bazzi S, Micallef E. Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon: a randomized, controlled study. *Clin Exp Rheumatol* 2001;19:503-8.
26 Herrick AL. Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. *Arthritis Rheum* 2011;63:775-82.
27 Schiopu E, Vivien M, Impens A, Rothman J, McCloskey D, Wilson J, et al. Randomized placebo-controlled crossover trial of tadalafil in Raynaud's phenomenon secondary to systemic sclerosis. *J Rheumatol* 2009;36:2264-8.
28 Shenoy P, Kumar S, Lalan KJ, Choudhary C, Singh U, Misra R, et al. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. *Rheumatology (Oxford)* 2010;49:2420-8.
29 Rosato E Borghese F, Pisarri S, Salsano F. Long-term therapy with NAC, in patients with SSc, has a durable effectiveness on ischemic ulcers and Raynaud's phenomenon. *Clin Rheumatol* 2009;28:1379-84.
30 Sambo P, Amico D, Giacomelli R, Matucci-Cerinic M, Salsano F, Valentini G, et al. Intravenous N-acetylcysteine for treatment of Raynaud's phenomenon secondary to systemic sclerosis: a pilot study. *J Rheumatol* 2001;28:2257-62.
31 Dziadzio M, Denton CP, Smith R, Howell A, Blann A, Bowers E, et al. Losartan therapy for Raynaud's phenomenon and scleroderma. *Arthritis Rheum* 1999;42:2646-55.
32 Gliddon A, Dore C, Black CM, McHugh N, Moots R, Denton CP, et al. Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon. *Arthritis Rheum* 2007;56:3837-46.
33 Wollershiem H, Thien T, Fennis J, Van Elteren P, Van't Laar A. Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. *Clin Pharmacol Ther* 1986;40:219-25.

Accepted: 05 January 2012

Cite this as: *BMJ* 2012;344:e289

Figures

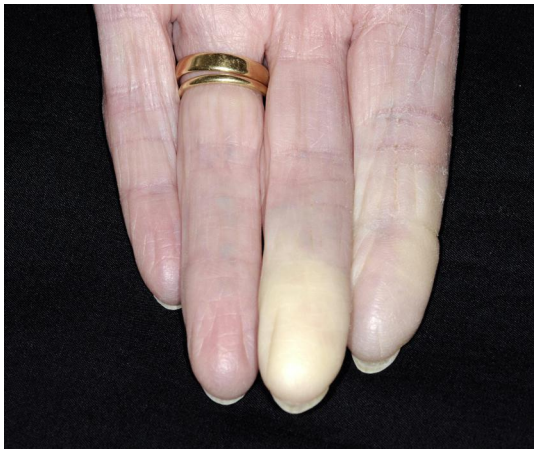

Fig 1 Raynaud's phenomenon showing typical colour changes

[Image: Dr P Marazzi/Science Photo Library]

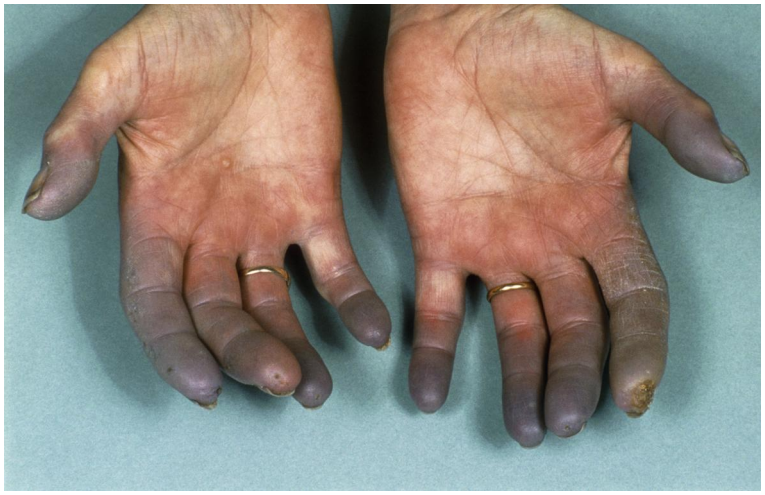

Fig 2 Severe Raynaud's phenomenon showing colour changes and digital ulceration

[Image: John Radcliffe Hospital/Science Photo Library]

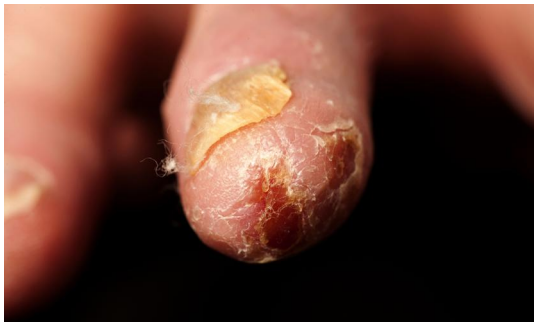

Fig 3 Digital ulcer in severe Raynaud's phenomenon